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A randomised, placebo-controlled, Phase II, dose-ranging trial of once-daily treatment with olodaterol, a novel long-acting β_2-agonist, for 4 weeks in patients with chronic obstructive pulmonary disease

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KEYWORDS
Olodaterol;
COPD;
Long-acting β_2-agonist;
Once-daily

Summary
Background: Olodaterol is a novel long-acting β_2-agonist (LABA) with ≥24-h duration of action in preclinical and clinical studies.
Objective: This Phase II, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-finding study evaluated four doses of once-daily olodaterol over 4 weeks in patients with chronic obstructive pulmonary disease (COPD), based on efficacy, safety and pharmacokinetic parameters.
Methods: Patients received olodaterol inhalation solution or placebo via Respimat® Soft Mist™ inhaler once daily for 4 weeks. Pulmonary function testing was performed pre-dose (trough) and up to 3 or 6 h post-dose, depending on visit. Primary end point was change from baseline in trough forced expiratory volume in 1 s (FEV_1) after 4 weeks' treatment. Secondary end points included change from baseline in peak FEV_1 and FEV_1 area under the curve from 0 to 6 h.

Abbreviations: AE, adverse event; AUC_{0-6}, area under the curve from 0 to 6 h; COPD, chronic obstructive pulmonary disease; C_{max}, maximum concentration; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; gCV, geometric coefficient of variation; LABA, long-acting β_2-agonist.

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Results: 405 patients with COPD were randomised and assigned to treatment. Mean baseline post-bronchodilator FEV_1 was 1.50 L (54% predicted). All olodaterol doses provided statistically significant increases in trough FEV_1 compared to placebo (2 μg: 0.061 L [$p = 0.0233$]; 5 μg: 0.097 L [$p = 0.0003$]; 10 μg: 0.123 L [$p < 0.0001$]; 20 μg: 0.132 L [$p < 0.0001$]). A clear dose—response relationship was demonstrated regarding pulmonary function; the two highest olodaterol doses (10 and 20 μg) formed the plateau of the dose—response curve. All olodaterol doses were well tolerated, with no dose-dependent safety effects.
Conclusion: Once-daily olodaterol demonstrated 24-h bronchodilator efficacy, confirming its potential as a once-daily LABA for the management of COPD.
Trial registration: ClinicalTrials.gov: NCT00452400.

Introduction

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity, mortality and health-care costs, with an estimated 65 million people worldwide experiencing moderate to severe disease activity according to World Health Organization estimates [1]. COPD is characterised by persistent and progressive airflow limitation, and is associated with chronic and progressive dyspnoea, cough and sputum production [2]. Treatment guidelines recommend the use of long-acting bronchodilators, such as long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists, for the maintenance treatment of patients with COPD when symptoms are not adequately controlled with short-acting agents [2]. The introduction of LABAs with a duration of action of ~12 h, nearly two decades ago, provided patients with superior bronchodilator efficacy and improved outcomes compared to that of shorter-acting agents [3,4]. Recently, several LABAs with a duration of action of ~24 h have been developed, providing the potential for once-daily pharmacotherapies that could offer improved treatment adherence as well as the opportunity for combination with other once-daily drugs such as tiotropium [5—8].

Olodaterol, which belongs to this new generation of LABAs, is characterised by enantiomeric purity, a high β_2-receptor selectivity and a near full agonist response at the human β_2-adrenoceptor *in vitro* [9]. In preclinical animal studies, olodaterol shows a rapid onset of action and inhibits acetylcholine-induced bronchospasms in anaesthetised guinea pigs and dogs [10]. Moreover, this bronchoprotective effect was demonstrated to last >24 h in both models [10].

This study is part of a series of trials designed to establish the optimum dose and treatment regimen for olodaterol in patients with COPD. An initial single-dose study demonstrated effective bronchodilation over 24 h for a range of olodaterol doses (2, 5, 10 and 20 μg) in a dose-dependent manner [11].

The primary objectives of this Phase II study were, therefore, to confirm the 24-h bronchodilator efficacy of olodaterol after once-daily administration in patients with COPD over an extended 4-week treatment period and to determine the most appropriate dose for the Phase III studies. The Phase III studies have now been performed and demonstrated the efficacy and tolerability of olodaterol 5 and 10 μg [12—15]. Additional objectives of this Phase II study were to evaluate the safety and tolerability of olodaterol as well as systemic pharmacodynamic and pharmacokinetic parameters.

Methods

Patients

Patients were enrolled if they met the following inclusion criteria: aged ≥40 years with a diagnosis of COPD [16]; current or ex-smokers with a smoking history of >10 pack-years; a post-bronchodilator forced expiratory volume in 1 s (FEV_1) of ≥30% and <80% of predicted normal; and a post-bronchodilator FEV_1/forced vital capacity (FVC) <70%. Key exclusion criteria were: a history of asthma; a history of myocardial infarction (within 1 year); clinically relevant cardiac arrhythmia; marked prolongation of QT/QTc interval (QTc interval >450 ms); regular use of daytime oxygen therapy; and use of β-adrenergic antagonists (β-blockers).

Study design

This was a Phase II, 4-week, multi-dose, multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group study registered with ClinicalTrials.gov (NCT00452400). Following an initial screening phase, patients entered a 2-week baseline period to ensure clinical stability (Fig. 1).

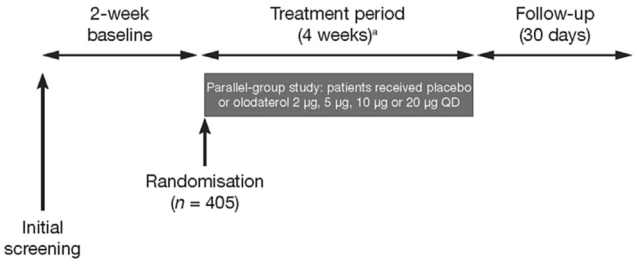


Figure 1 Study design.

Eligible patients were randomly assigned to 4 weeks of double-blind treatment, in which they received an inhalation solution containing one of four olodaterol doses (2, 5, 10 or 20 μg), or placebo, delivered by the Respimat® Soft Mist™ inhaler. Each administration of olodaterol comprised two actuations from the Respimat® device. Patients were evaluated for an additional 30 days following completion of the randomised treatment period. Patients were permitted to use inhaled corticosteroids, short-acting anticholinergics and low doses of oral corticosteroids (equivalent to prednisone ≤10 mg/day or 20 mg prednisone every other day) if stabilised for 6 weeks prior to screening. Concomitant use of methylxanthines, long-acting anticholinergic drugs and LABAs (other than the study drug) was not allowed. Salbutamol was provided for use as a rescue medication if required.

The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines and local regulatory requirements. Prior to study initiation, the protocol was approved by the ethics research board of the respective institutions and signed consent was obtained from all patients.

Assessments

Spirometry

At screening, the qualifying pulmonary function test and reversibility testing using salbutamol were conducted. Spirometry (FEV_1, FVC) was used to assess primary and secondary end points and was performed according to American Thoracic Society and European Respiratory Society criteria using the VIASYS™ Healthcare MasterScope [17]. Pulmonary function tests were performed at 1 h and 10 min pre-dose and at 30 min, 1, 2 and 3 h post-dose on Day 1 (first dose), Day 8, Day 15 and Day 29. Additionally, on Day 29, pulmonary function tests were performed at 4, 5 and 6 h post-dose.

The primary end point was trough FEV_1 response (L) determined at the end of the 4-week treatment period (Day 29). Trough FEV_1 was defined as the mean of two pre-dose FEV_1 values (−1 h, −10 min) (i.e. FEV_1 at the end of the 24-h dosing interval). Trough FEV_1 response was defined as the change from baseline FEV_1, which was defined as the mean of the FEV_1 value 1 h prior and 10 min prior to inhalation of the first dose of randomised treatment. Secondary end points included: peak FEV_1 response; FEV_1 area under the curve from 0 to 6 h (AUC_{0-6}) response (Day 29); trough and peak FVC response; and FVC AUC_{0-6} response (Day 29). The severity of COPD symptoms (wheezing, shortness of breath, coughing and tightness of chest) was recorded in electronic case report forms using the scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. Scores were based on investigators' assessment of patients' condition in the week prior to the clinic visit and were evaluated prior to the assessment of pulmonary function.

Safety assessments

Adverse events (AEs) were monitored and recorded at each patient visit. Safety measurements including vital signs (blood pressure and pulse rate), 12-lead electrocardiogram and clinical laboratory tests were conducted on all patients at screening and each subsequent treatment visit. Plasma potassium and creatinine phosphokinase were measured as systemic pharmacodynamic parameters. Other observations included COPD symptom scores, Physician's Global Evaluation, use of concomitant therapies and the need for test-day rescue medication (salbutamol).

Pharmacokinetic assessments

Plasma concentrations of olodaterol and known metabolites were assessed on Days 1, 8, 15 and 29 using 9—10 mL of blood taken from a forearm vein prior to and following drug inhalation. Urine samples were collected prior to and following drug administration on Days 1 and 29. Plasma and urine olodaterol concentrations were validated by high-performance liquid chromatography, coupled to tandem mass spectrometry assays.

Statistical analysis

The planned sample size of 80 evaluable patients per group provided ≥90% power to detect a difference of 0.12 L from placebo at the 5% level of significance (two-sided) [18], assuming a standard deviation for trough FEV_1 of 0.229 L. The full analysis set was defined as all patients who were randomised, had received at least one dose of study treatment and had a valid baseline measurement for at least one end point. The primary and secondary end points were analysed using analysis of covariance, which compared the bronchodilator efficacy of the five treatments, as determined by trough FEV_1 response (L) after 4 weeks of randomised therapy. In this analysis, 'baseline trough FEV_1' was a linear covariate, 'treatment' was a fixed effect and 'centre' was a random effect.

Pharmacokinetic analysis of the plasma/urine concentration-time data was carried out by non-compartmental analysis using the WinNonlin™ software program (Professional, Version 5.2, Pharsight Corporation, Mountain View, California, USA). All randomised patients who received at least one dose of study medication were included in the safety evaluation, which was analysed using descriptive statistical methods.

Results

Patient population

The trial was conducted between 12 March 2007 and 14 January 2008. A total of 621 patients were enrolled at 42 centres in four countries: Canada, Germany, The Netherlands and the USA. Of those patients, 405 were randomised and treated (Fig. 2 and Table 1).

In total, 17 patients prematurely discontinued from the trial, the majority due to AEs. The average screening post-bronchodilator FEV_1 was 1.50 L (54% predicted normal). In general, baseline patient characteristics were comparable across treatment groups (Table 2).

Efficacy

Lung function

All olodaterol doses were significantly superior to placebo for the primary efficacy end point of trough FEV_1 response

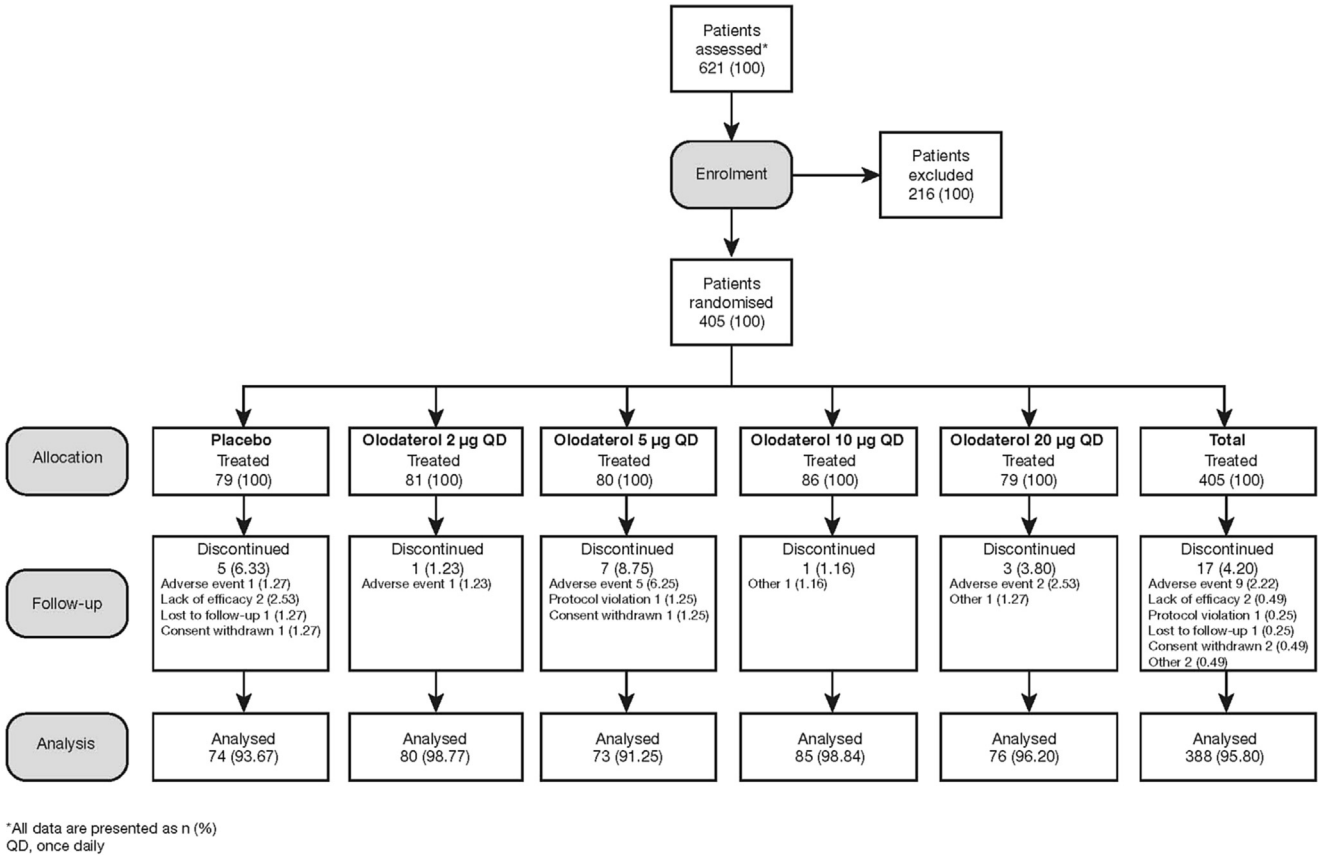


Figure 2 CONSORT diagram illustrating patient flow.

following 4 weeks of treatment (difference from placebo 0.061 L for 2 µg [$p = 0.0233$], 0.097 L for 5 µg [$p = 0.0003$], 0.123 L for 10 µg [$p < 0.0001$] and 0.132 L for 20 µg [$p < 0.0001$]) (Table 2). A clear dose—response relationship between 2, 5 and 10 µg olodaterol treatments was evident, with a more modest increase seen with 20 µg olodaterol compared to 10 µg at Week 4 (Table 2 and Fig. 3).

FEV_1 trough responses confirmed the 24-h bronchodilator activity. All olodaterol doses demonstrated a statistically significant increase versus placebo ($p < 0.002$) in FEV_1 at all time points post-dose after the first dose and after 1, 2 and 4 weeks of treatment (Fig. 3).

All doses of olodaterol were superior to placebo for peak FEV_1 and FEV_1 AUC_{0-6} following 4 weeks of olodaterol treatment (Table 2). The statistically significant improvements ($p < 0.001$) in peak FEV_1 compared to placebo were observed after the first dose and were maintained over the 4-week treatment period. Overall, there was an indication of increased efficacy with increasing dose for 2, 5 and 10 µg over the treatment period, with no further increase in efficacy observed with 20 µg compared to 10 µg. All doses of olodaterol were statistically superior to placebo for FVC trough, peak and AUC_{0-6} with the exception of trough FVC for olodaterol 2 µg (Fig. 4 and Table 3).

Increased efficacy with 5, 10 and 20 µg doses of olodaterol compared to 2 µg was observed but a clear dose-ordering effect was less apparent. The FVC time profiles following olodaterol administration followed a similar pattern to the FEV_1 data (Fig. 4). The differences from baseline 3 h after the first olodaterol dose were similar to those after 4 weeks of treatment. A dose-dependent effect on FVC AUC_{0-6} was evident between 2, 5 and 10 µg olodaterol. A slight reduction in FVC AUC_{0-6} and peak FVC was observed for 20 µg olodaterol compared to 10 µg, in line with the plateau observed at these doses for FEV_1.

COPD symptom scores

COPD symptom scores were generally around the "Mild" level (score of 1) for coughing and shortness of breath, and between "None" and "Mild" for tightness of chest and wheezing. The results for shortness of breath and wheezing showed small improvements with olodaterol compared to placebo but the differences were generally not statistically significant. Most groups demonstrated statistically significant improvements in shortness of breath at Week 1 and wheezing at Week 2 ($p < 0.05$). There was no significant improvement in cough or tightness of chest over the course of the trial.

Safety

All olodaterol doses were well tolerated with no apparent dose-dependent AEs over the 4-week treatment course (Table 4); the number of patients who experienced any AE during the trial was balanced across treatment groups.

Nasopharyngitis was reported in one patient in the placebo group and a total of 14 patients in the olodaterol groups. However, no dose-dependent effect was observed, e.g. nasopharyngitis occurred in two patients in both the 2 µg

Table 1 Patient demographics and baseline characteristics.

	Placebo	Olodaterol			
	(n = 79)	2 μg QD (n = 81)	5 μg QD (n = 80)	10 μg QD (n = 86)	20 μg QD (n = 79)
Sex, n (%)					
Male	39 (49.4)	42 (51.9)	56 (70.0)	51 (59.3)	46 (58.2)
Female	40 (50.6)	39 (48.1)	24 (30.0)	35 (40.7)	33 (41.8)
Mean (SD) age, years	62.7 (9.7)	63.8 (8.6)	63.3 (9.5)	63.6 (7.9)	63.2 (9.0)
Smoking status, n (%)					
Current smokers	41 (51.9)	40 (49.4)	34 (42.5)	46 (53.5)	41 (51.9)
Ex-smokers	38 (48.1)	41 (50.6)	46 (57.5)	40 (46.5)	38 (48.1)
Mean (SD) smoking, pack-years	50.0 (25.0)	46.0 (20.9)	49.0 (25.1)	43.6 (18.5)	47.6 (23.3)
Post-bronchodilator screening[a]					
Mean (SD) FEV_1, L	1.45 (0.47)	1.49 (0.47)	1.55 (0.50)	1.54 (0.53)	1.48 (0.53)
Mean (SD) % predicted normal FEV_1	53.9 (12.7)	55.2 (13.4)	52.8 (13.6)	55.0 (12.9)	54.0 (13.3)
Mean (SD) FVC, L	2.87 (0.86)	2.95 (0.88)	3.14 (0.96)	3.04 (0.99)	2.93 (0.94)
Mean (SD) FEV_1/FVC, %	51.67 (11.65)	51.12 (9.93)	50.38 (10.90)	51.58 (10.19)	51.15 (10.62)
Mean (SD) FEV_1 % change from pre-bronchodilator	14.4 (14.0)	15.9 (12.0)	19.9 (16.5)	17.5 (12.7)	17.8 (15.8)
Pulmonary medications at baseline, n (%)					
Short-acting anticholinergic[b]	17 (21.5)	27 (33.3)	20 (25.0)	19 (22.1)	20 (25.3)
Long-acting anticholinergic[c]	13 (16.5)	7 (8.6)	18 (22.5)	15 (17.4)	9 (11.4)
Short-acting β-adrenergic[d]	42 (53.2)	55 (67.9)	50 (62.5)	45 (52.3)	52 (65.8)
Long-acting β-adrenergic[e]	27 (34.2)	38 (46.9)	35 (43.8)	35 (40.7)	34 (43.0)
Inhaled corticosteroid[b]	39 (49.4)	40 (49.4)	37 (46.3)	43 (50.0)	37 (46.8)

QD, once daily; SD, standard deviation.
[a] 10–15 min after 400 μg of salbutamol.
[b] Permitted to continue throughout trial.
[c] Not permitted during any part of the study.
[d] Permitted as rescue medication during study.
[e] Permitted during baseline and follow-up periods only.

and 20 μg dose groups. The majority of AEs were mild to moderate in nature, with only a small number of serious AEs reported during the trial (eight patients). Serious AEs were COPD exacerbation (two patients) and fall, acute sigmoid diverticulitis, upper respiratory tract infection, bronchitis, pleural effusion, gastrointestinal bleeding, road traffic accident, hip fracture, humerus fracture and lung cancer in one patient each, with no indication that they were related to the administration of olodaterol. A small number of AEs occurred with a frequency of >3%, the most common included nasopharyngitis, upper respiratory tract infection, bronchitis, headache, dyspnoea, cough and COPD exacerbations (Table 4). There were no fatal events associated with this study. AEs leading to discontinuation were recorded in nine patients and were palpitations, sinusitis, syncope, vasovagal syncope, cough, hip fracture, fatigue, dyspnoea, gastrointestinal bleeding and upper respiratory tract infection in one patient each, and COPD in two patients, none of which were considered to be related to the study treatment. No dose-dependent relationship was evident with the small number of AEs leading to discontinuation.

Serum potassium levels for 2, 5 and 10 μg olodaterol after the first dose were similar to placebo. In contrast, there were small but statistically significant ($p < 0.01$) reductions in serum potassium levels for 20 μg olodaterol compared to placebo at both 1 and 3 h post-dose. After 4 weeks of treatment, there were no statistically significant differences in serum potassium levels at any dose versus placebo, although with 20 μg olodaterol at 1 h post-dose, a near-significant effect was observed ($p = 0.068$). A similar pattern was observed for creatinine phosphokinase, another marker of pharmacodynamic activity.

No dose-dependent changes in systolic and diastolic blood pressure or pulse rate were observed in any dose groups during treatment. Results from the 12-lead electrocardiogram showed no dose-dependent effects of olodaterol administration on heart rate. Changes from baseline for QT and QTcF showed no consistent pattern across the dose groups.

Pharmacokinetics

Plasma concentrations of olodaterol and its metabolites were mostly below the limit of quantification for olodaterol 2 μg. In the 5–20 μg olodaterol dose groups, olodaterol and olodaterol–glucuronide plasma maximum concentrations (C_{max}) were observed after ~10 min and 3 h, respectively, following single and repeated inhalation. Olodaterol plasma concentrations declined rapidly and represented ~37–56% of C_{max} at 6 h on Day 29 following inhalation of 10 and 20 μg olodaterol. Renal excretion of olodaterol was low and varied from 0.341% (geometric coefficient of variation [gCV] 182%) to 0.510% (gCV 102%) of the dose on Day 1, and between 0.628% (gCV 118%) to 0.814% (gCV 102%) of the dose on Day 29. Systemic exposure parameters of olodaterol, steady-state C_{max} and steady-state area under the curve from 0 to 1 h increased proportionally within the 5–20 μg dose range.

Table 2 Adjusted mean (standard error) FEV_1 response (trough, peak, AUC_{0-6}) after 4 weeks of treatment (Day 29).

Treatment	Trough FEV_1			Peak FEV_1			FEV_1 AUC_{0-6}		
	Response	vs placebo	*p* value	Response	vs placebo	*p* value	Response	vs placebo	*p* value
Placebo	−0.014 (0.021)			0.078 (0.026)			0.013 (0.025)		
Olodaterol 2 μg QD	0.046 (0.021)	0.061 (0.027)	0.0233	0.242 (0.026)	0.164 (0.034)	<0.0001	0.154 (0.024)	0.141 (0.032)	<0.0001
Olodaterol 5 μg QD	0.082 (0.021)	0.097 (0.027)	0.0003	0.247 (0.026)	0.169 (0.034)	<0.0001	0.175 (0.025)	0.162 (0.032)	<0.0001
Olodaterol 10 μg QD	0.109 (0.021)	0.123 (0.026)	<0.0001	0.295 (0.025)	0.218 (0.034)	<0.0001	0.226 (0.024)	0.213 (0.031)	<0.0001
Olodaterol 20 μg QD	0.118 (0.021)	0.132 (0.027)	<0.0001	0.303 (0.026)	0.225 (0.034)	<0.0001	0.228 (0.025)	0.214 (0.032)	<0.0001

QD, once daily.

Discussion

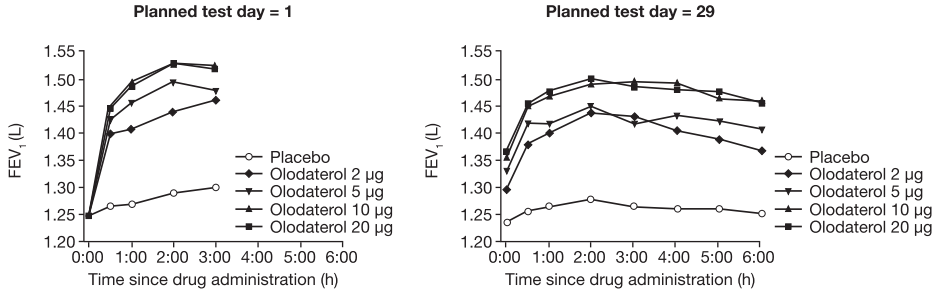
The findings from this 4-week, multi-dose study provide further evidence of the 24-h bronchodilator efficacy of olodaterol and support once-daily administration in patients with moderate to severe COPD. Statistically superior improvements in peak FEV_1, FEV_1 AUC_{0-6} and trough FEV_1 responses were observed with all once-daily doses of olodaterol compared to placebo, following 4 weeks of treatment. Trough FEV_1 response was selected as the primary end point for this study, as this measure gives the best indication of potential for 24-h bronchodilator activity. Hence, the consistent trough FEV_1 improvement across all measured time points supports the potential for once-daily dosing with olodaterol. The limited improvements in symptom score may be a result of the small size of the study, and relatively low sensitivity of the scoring system.

These findings extend previous study results after single-dose administration in patients with COPD and those with asthma [11,19], by providing an integrated overview of multiple efficacy measures (trough, peak and AUC_{0-6}) that can be interpreted to gain an overview of the bronchodilatory effect of olodaterol. Similar findings have been reported in Phase II studies of tiotropium in patients with COPD, with comparable improvements in trough, peak and average FEV_1, and in trough:peak FEV_1 ratios [20,21], to those observed in the current olodaterol study.

Investigation of a range of doses allowed characterisation of the olodaterol dose–response curve. A clear dose–response relationship was observed with respect to pulmonary function for the tested dose range (2–20 μg olodaterol) after 4 weeks of olodaterol treatment and improvements in FVC supported those observed for FEV_1.

Importantly, the study identified where the slope and plateau of the dose–response curve lie. Taking into account all the results from the pulmonary function parameters in this study, the efficacy of 10 and 20 μg olodaterol were relatively similar, suggesting that both doses represent a plateau in therapeutic effect. These olodaterol doses showed a consistent increase in efficacy compared to 2 μg, suggesting that 2 μg is on the steep portion of the dose–response curve. However, limitations do exist in terms of the precision of characterisation of the dose–response curve because the study was powered to identify an effect versus placebo and not to identify statistically significant differences between olodaterol doses. For example, while there is a clear distinction between the 2 μg dose and 10 or 20 μg doses, the positioning of the 5 μg dose with respect to 2 and 10 μg is less clear. Further evaluation of the dose–response curve was warranted, therefore, by incorporating 5 μg and 10 μg doses in Phase III investigations.

The findings of this study regarding the olodaterol dose–response curve are broadly similar to those observed in another Phase II investigation of olodaterol (1222.3; NCT01809262). However, in that study, the separation between the 10 μg and 20 μg doses was greater than in the current investigation. This may be explained by the differences in study design and patient inclusion criteria. For example, 1222.3 was a single-dose, five-way



Means adjusted for test day baseline, treatment and centre (centre random, all other effects fixed);
common baseline mean (standard error): 1.25 (0.48) L
$p < 0.001$ for all olodaterol doses vs placebo, at all time points post-dose, after the first dose and at Week 4 (Day 29)
At Day 29, $p < 0.01$ for trough FEV_1 olodaterol 20 µg vs 2 µg; all other dose comparisons did not reach significance

Figure 3 Adjusted mean FEV_1 (L): individual time points from 0 to 3 h after first dose (Day 1) and 0—6 h after 4 weeks of treatment (Day 29).

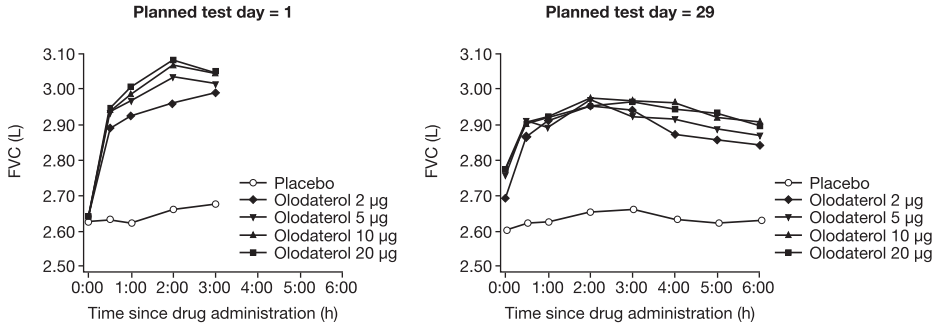
crossover study that required patients to meet reversibility criteria, specifically a bronchodilator responsiveness of 12% from baseline FEV_1 45 min after inhalation of salbutamol. In contrast, the current study did not use the results of reversibility testing as an inclusion criterion.

The present study demonstrated acceptable short-term safety and tolerability profiles for once-daily olodaterol treatment over 4 weeks in patients with COPD. The occurrence of AEs was low, with mostly mild to moderate intensities, equally distributed across all treatment groups.

The known systemic pharmacodynamic effects of LABAs assist in the selection of appropriate doses for analysis of efficacy. The dose-selection process in the current study comprised assessment of efficacy across a range of olodaterol doses, in parallel with investigation of systemic pharmacodynamic parameters known to be sensitive to β_2-agonists. This allowed clear identification of the dose lying on the steep portion of the dose—response curve for efficacy, the position of the plateau of this curve and also the identification of the threshold of systemic pharmacodynamic activity. There was little evidence for systemic pharmacodynamic activity at the doses studied, with the exception of small reductions in serum potassium concentrations at 20 µg olodaterol. Based on these considerations and the satisfactory safety and tolerability profiles observed, doses of 5 and 10 µg olodaterol were selected for Phase III clinical trials which demonstrated a 24-h bronchodilatory profile and satisfactory tolerability in patients with moderate to very severe COPD [12—15]. Olodaterol has been approved for use in COPD in several countries.

Non-adherence to medication represents a significant barrier to optimal disease management in COPD [22]. Hence, uncomplicated medication regimens with a reduced dosing frequency should improve adherence by making treatment more convenient [23]. Currently, a number of new longer-acting β_2-adrenoceptor agonists, of which indacaterol is the first approved (in the EU, USA and Canada), are under clinical development with the objective of achieving once-daily dosing.

The current investigation, in combination with study 1222.3, established an appropriate lowest efficacious dose of olodaterol, and the 24-h bronchodilator efficacy observed suggested that once-daily posology may be a viable strategy. This could prove advantageous for patients in the advanced stages of COPD for whom combination therapy with once-daily long-acting anticholinergics is indicated to maximise bronchodilation. However, the fact that olodaterol demonstrates sufficient 24-h bronchodilator efficacy does not necessarily define it as a once-daily treatment. A further Phase II investigation, study 1222.26 (NCT00846768), was conducted to assess the efficacy of both once- and twice-daily dosing regimens [24]; this,



Means adjusted for test day baseline, treatment and centre (centre random, all other effects fixed);
common baseline mean (standard error): 2.60 (0.86) L
$p < 0.001$ for all olodaterol doses vs placebo, at all time points post-dose, after the first dose and at Week 4 (Day 29)
At Day 29, olodaterol dose comparisons for FVC AUC_{0-6} did not reach significance

Figure 4 Adjusted mean FVC (L): individual time points from 0 to 6 h after first dose (Day 1) and after 4 weeks of treatment (Day 29).

Table 3 Adjusted mean (standard error) FVC response (trough, peak, AUC_{0-6}) after 4 weeks of treatment (Day 29).

Treatment	Trough FVC			Peak FVC			FVC AUC_{0-6}		
	Response	vs placebo	*p* value	Response	vs placebo	*p* value	Response	vs placebo	*p* value
Placebo	−0.026 (0.040)			0.152 (0.046)			0.009 (0.044)		
Olodaterol 2 μg QD	0.068 (0.040)	0.094 (0.051)	0.0695	0.440 (0.046)	0.288 (0.061)	<0.0001	0.271 (0.043)	0.262 (0.057)	<0.0001
Olodaterol 5 μg QD	0.136 (0.040)	0.162 (0.052)	0.0018	0.432 (0.046)	0.280 (0.062)	<0.0001	0.292 (0.044)	0.283 (0.057)	<0.0001
Olodaterol 10 μg QD	0.146 (0.039)	0.172 (0.051)	0.0008	0.449 (0.044)	0.297 (0.061)	<0.0001	0.320 (0.042)	0.311 (0.056)	<0.0001
Olodaterol 20 μg QD	0.153 (0.040)	0.179 (0.052)	0.0006	0.438 (0.046)	0.286 (0.062)	<0.0001	0.313 (0.044)	0.304 (0.057)	<0.0001

QD, once daily.

Table 4 Summary of AEs with an incidence of >3%.

Event	Placebo, n (%)	Olodaterol 2 μg QD, n (%)	Olodaterol 5 μg QD, n (%)	Olodaterol 10 μg QD, n (%)	Olodaterol 20 μg QD, n (%)
Total treated	79 (100)	81 (100)	80 (100)	86 (100)	79 (100)
Total with any AE	29 (36.7)	30 (37.0)	33 (41.3)	26 (30.2)	30 (38.0)
Nasopharyngitis	1 (1.3)	2 (2.5)	6 (7.5)	4 (4.7)	2 (2.5)
Upper respiratory tract infection	1 (1.3)	0 (0.0)	2 (2.5)	1 (1.2)	4 (5.1)
Bronchitis	0 (0.0)	1 (1.2)	3 (3.8)	2 (2.3)	0 (0.0)
Headache	4 (5.1)	3 (3.7)	1 (1.3)	3 (3.5)	1 (1.3)
Dyspnoea	6 (7.6)	3 (3.7)	2 (2.5)	0 (0.0)	3 (3.8)
Cough	2 (2.5)	4 (4.9)	6 (7.5)	2 (2.3)	2 (2.5)
COPD exacerbation	2 (2.5)	3 (3.7)	2 (2.5)	4 (4.7)	2 (2.5)

QD, once daily.

together with other olodaterol data, led to the development of olodaterol as a once-daily agent.

Conflicts of interest

Alan L Hamilton, Lawrence Korducki and Paul Koker are employees of Boehringer Ingelheim. M. Reza Maleki-Yazdi, Ekkehard Beck and Charles Fogarty disclose no conflicts of interest.

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